Bromocriptine and Lisuride in Parkinson Disease

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Lisuride was compared with bromocriptine in 25 parkinsonian patients in whom the response to levodopa had diminished; 19 had "wearing off," "on-off" phenomena, or both. At the time bromocriptine was added to levodopa, the mean age of the patients was 62.7 years and mean disease duration was 8.9 years. Disability decreased by 34% in the on period and by 20% in the off period, and the number of hours the patients were on increased from 9.6 to 12.8. All these changes were significant ($p \leq 0.01$ to 0.05). Bromocriptine, however, had to be discontinued in 11 patients because of adverse effects. In the remaining 14 patients, bromocriptine was eventually discontinued because of decreased efficacy. Mean dose of bromocriptine was 55 mg (range, 20 to 100 mg).

At the time lisuride was added to levodopa the patients were older (65.4 years), had had the disease longer (11.4 years), and were more disabled. Nonetheless, disability decreased in the on period by 33% and in the off period by 17%, and the number of hours the patients were on increased from 3.9 to 8.9. All these changes were significant ($p \leq 0.01$ to 0.05). The mean dose of lisuride was 2.8 mg (range, 0.6 to 5.0 mg). Lisuride was discontinued in 8 patients because of adverse effects.

Both bromocriptine and lisuride are useful in managing patients with advanced Parkinson disease whose response to levodopa has diminished. While it is presently not possible to state which of the drugs is more effective, ultimately their usage will probably be determined by their relative cost.

Lieberman AN, Gopinathan G, Neophytides A, Leibowitz M, Walker R, Hiesiger E: Bromocriptine and lisuride in Parkinson disease. Ann Neurol 13:44–47, 1983

In Parkinson disease, the striatal dopamine (DA) content is decreased in proportion to the degree of degeneration of DA-containing neurons in the substantia nigra [1]. Levodopa therapy depends upon the capacity of the remaining neurons to synthesize DA in sufficient quantities to stimulate the striatal DA receptors [3, 5].

Following chronic treatment with levodopa, degeneration of the nigrostriatal neurons may eventually proceed to the point that remaining cells can no longer synthesize sufficient dopamine to stimulate striatal receptors. Consequently, the response to levodopa decreases and is accompanied by diurnal oscillations in performance: "wearing off" or "on-off" phenomena or a combination [12, 13]. At least theoretically, such patients might benefit from drugs that stimulate the striatal receptors directly, i.e., DA agonists. Bromocriptine, an ergoline polypeptide, was shown to have the properties of a DA agonist stimulating the non-cyclase-linked striatal DA receptors (D_2 receptors) [15, 16]. However, bromocriptine's activity depends in part on presynaptic DA synthesis [4]. While about half of treated patients improve, the incidence of adverse effects is high, as is the cost of the drug [2, 11].

Lisuride hydrogen maleate is a semisynthetic ergot alkaloid that also stimulates the non-cyclase-linked striatal DA receptors and has been found effective in Parkinson disease [6, 9, 10, 16]. Lisuride is ten times more potent than bromocriptine on a milligram per milligram basis, its activity is independent of presynaptic DA synthesis, and it also acts as a central serotonin agonist. Thus, lisuride might be useful in patients with extensive degeneration of the presynaptic nigrostriatal neurons whose response to levodopa and bromocriptine has diminished. Furthermore, the drug is less expensive to produce than bromocriptine, which may become an important consideration for some patients. We have treated 25 parkinsonian patients first with bromocriptine and subsequently with lisuride. This study compares the results.

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Received Jan 29, 1982, and in revised form Apr 2. Accepted for publication Apr 9, 1982.

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 0364-5134/83/010044-04$1.50

Methods

Between June 15, 1979, and December 31, 1981, 25 patients who had been treated earlier with bromocriptine in addition to levodopa were given lisuride in addition to levodopa. The best response of these 25 patients during their bromocriptine and levodopa therapy was compared retrospectively with their best response on lisuride and levodopa.

Bromocriptine Treatment

When the 25 patients started taking bromocriptine, their mean age was 62.7 years (range, 50 to 76 years) and the mean duration of Parkinson disease was 8.9 years (range, 1 to 14 years). All 25 had been treated with levodopa alone or combined with carbidopa (Sinemet). Twenty-one of the 25 patients had, at some point, improved on levodopa. In time, however, the response had declined in all the patients and 6 were worse than before starting levodopa. The mean duration of levodopa treatment was 6.2 years (range, 1 to 12 years). Nineteen patients developed "wearing off" or "on-off" phenomena (or both). Attempts to increase levodopa augmented dyskinesias or aggravated on-off phenomena; attempts to rearrange the timing of the doses of levodopa or the ratio of levodopa to carbidopa were only transiently helpful; and attempts to decrease levodopa resulted in worsening parkinsonian symptoms. Ten patients had participated in levodopa "drug holidays" of 7 to 14 days' duration with limited benefit. All the patients had, at one time, been treated with amantadine or an anticholinergic drug, but only 7 were still taking them. These drugs were continued unchanged throughout the study.

After informed consent was obtained, bromocriptine was started at a dose of 5 to 10 mg per day. It was increased by 5 to 10 mg daily in inpatients and by 5 to 10 mg daily each week in outpatients until toxicity appeared. Initially, no attempt was made to decrease the dose of levodopa, but later, because of additive adverse effects, the dosage was decreased in some patients.

Lisuride Treatment

All 25 patients were older at the time lisuride treatment was initiated than when bromocriptine was started—65.4 years (range, 50 to 82 years)—and had had Parkinson disease longer—11.4 years (range, 4 to 18 years). Lisuride was begun at a dose of 0.1 mg once a day. The dosage was increased by 0.1 to 0.4 mg per day until adverse reactions occurred or an arbitrary maximum of 5 mg per day was attained. Bromocriptine was discontinued for at least 1 to 3 days before lisuride was started. Laboratory evaluations included hemogram, tests of liver and renal function, and cardiac evaluation.

Neurological Assessment

Before beginning bromocriptine or lisuride therapy, the patients were examined on a daily basis by a neurologist who was neither aware of the medications they were receiving nor responsible for their care. The neurologist assessed the signs of the disease during both on and off periods using a standardized parkinsonian disability scale, which is fully described elsewhere [8]. On this scale 0 represents no disability and 100% represents maximum disability. Patients were also staged on the scale of Hoehn and Yahr. Wearing off and on-off phenomena were assessed as previously described, with a trained nurse or neurologist recording the number of hours the patients were on and mobile [8]. Upon completion of the initial 4- to 8-week in-hospital evaluation, patients were seen at 1- to 2-month intervals. Statistical analysis was performed using the paired t test to the 5% level of significance.

Results

Drug Effect on Parkinsonian Disability Score in the On Period

BROMOCRIPTINE. The best mean parkinsonian disability score for the 25 patients taking levodopa was 33.5 ± 3.2 after 6.2 years of treatment. The score declined by 34% to 22.0 ± 2.7 with bromocriptine; this change is significant at 1%. The mean stage of the patients taking levodopa alone was 3.0 ± 0.1 and decreased to 2.5 ± 0.1 with bromocriptine. Nine of 25 patients (36%) improved by at least one stage. The mean dose of levodopa (in Sinemet) before the patients started taking bromocriptine was 1,200 mg and decreased to 935 mg with bromocriptine. The mean bromocriptine dose was 55 mg (range, 20 to 100 mg). The mean duration of treatment was 21 months (range, 1 to 65 months).

LISURIDE. The best mean parkinsonian disability score for the 25 patients taking levodopa was 49.4 ± 3.0 after 8.9 years of treatment. The score decreased by 33% to 33.5 ± 3.4 with lisuride; this change is significant at the 1% level. The mean stage of the patients taking levodopa was 3.7 ± 0.2, and decreased to 3.2 ± 0.1 with lisuride. Eleven of the 25 patients (44%) improved by at least one stage. The mean dose of levodopa (in Sinemet) before lisuride therapy started was 1,000 mg and decreased to 900 mg with lisuride. The mean lisuride dose was 2.8 mg (range, 0.6 to 5.0 mg). The mean duration of treatment was 12.1 months (range, 1 to 30 months).

Drug Effect on Parkinsonian Disability Score in the Off Period

BROMOCRIPTINE. The best mean parkinsonian disability score for the 25 patients taking levodopa as assessed in the off period was 55.0 ± 4.0 and decreased by 20% to 44.0 ± 4.0 with bromocriptine. This difference is significant at 5%. The mean stage for the 19 patients taking levodopa was 4.0 ± 0.1 and decreased to 3.7 ± 0.1 with bromocriptine. Five of 19 patients (26%) improved by at least one stage.

LISURIDE. The best mean parkinsonian disability score for the 25 patients taking levodopa as assessed in the off period was 70.3 ± 3.2 and decreased by

17% to 58.1 ± 2.8 with lisuride. This difference is significant at the 1% level. The mean stage of the patients taking levodopa alone was 4.7 ± 0.4 and decreased to 4.2 ± 0.2 with lisuride. Nine of 19 patients (47%) improved by at least one stage.

Drug Effect on Number of Hours On

BROMOCRIPTINE. The mean number of hours on for the 19 patients with wearing off or on-off phenomena (or both) on levodopa was 9.6 ± 0.6 and increased by 33% to 12.8 ± 0.8 with bromocriptine. This change is significant at 1%.

LISURIDE. The mean number of hours on for the 19 patients taking levodopa was 3.9 ± 0.4 and increased by 128% to 8.9 ± 0.9 with lisuride. This change is significant at 1%.

Adverse Reactions Necessitating Discontinuation of the Drug

Eleven of 25 patients discontinued bromocriptine because of adverse effects: 9 on account of an organic confusional syndrome, 1 because of dyskinesias, and 1 because of peripheral edema. Eight of 25 patients discontinued lisuride because of adverse effects: 5 because of mental changes, 2 because of dyskinesias, and 1 because of digital vasospasm.

Discussion

This study demonstrates that bromocriptine and lisuride are useful adjuvants to levodopa therapy in patients who are no longer satisfactorily responding to levodopa alone. Treatment with lisuride was begun after bromocriptine, at a time when the patients were considerably more disabled. Using bromocriptine first and then lisuride improved our patients' condition for a total of three years. Because the activity of lisuride (unlike bromocriptine) is independent of presynaptic nigrostriatal DA synthesis, lisuride may be the preferred drug in patients with more advanced disease and extensive degeneration of the nigrostriatal system. Our study suggests that giving bromocriptine first and then lisuride may be the preferred sequence. However, another study in which this sequence was not followed and in which the drugs were compared in patients with similar disabilities suggests that the drugs are equally effective (i.e., sequencing is not important) [7]. Although there may (or may not) be advantages to using one drug first, unfortunately it is likely that cost considerations will ultimately determine usage. Lisuride resulted in a greater increase in the number of hours on. Because lisuride has a shorter half-life than bromocriptine [14], this increase suggests that intracerebral mechanisms, occurring at the level of the DA receptor, may be more important in determining oscillations in performance than are plasma levels of the drug.

Adverse effects of lisuride were comparable to those of bromocriptine. Thus, of 11 patients who stopped taking bromocriptine because of adverse effects, 9 discontinued it because of mental changes, while 5 of 8 who discontinued lisuride did so because of mental changes. However, it should be noted that some of the patients who experienced mental changes during bromocriptine therapy did not experience similar changes with lisuride. Orthostatic hypotension and erythroderma were more common with bromocriptine, while dyskinesias and peripheral edema were more common with lisuride.

Although both bromocriptine and lisuride are predominantly D_2 receptor agonists, differences between them may include the following: (1) binding characteristics at the D_2 receptor (i.e., relative affinity for the receptor, requirement for cofactors); (2) ability to act as partial agonists (or antagonists) at other receptors (the D_1 receptor, the presynaptic autoreceptor, the serotonin receptor); (3) ability of their metabolites to act as partial agonists (or antagonists) at the different receptors; and (4) requirement for presynaptic DA synthesis. There may be enough differences between bromocriptine and lisuride to suggest that a combination of the two may be better than either alone. Recently (since completion of the present study), we had the opportunity to combine lisuride with bromocriptine in 3 patients. The response of 2 of these patients to this combination was considerably better than it had been to either drug alone. As current treatment for Parkinson disease is palliative and not curative, it would be desirable, cost notwithstanding, to have both drugs available and use them singly or in combination as circumstances dictate.

The authors wish to thank Eileen Boyd, RN, Clare Strohsahl, RN, Bernadette Hargin, RN, and the staff of 10 East for their help in evaluating the patients, and Kathleen Faridazar, MA, for help in preparing the manuscript.

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